n and n_1 are independently 1-8, provided that either R_1 is Q or R_2 is Q'.

REMARKS

The Office Action has rejected Claims 42-48 and 51 under 35 U.S.C. §112, first paragraph, alleging that the specification is not enabling for treating all cancers. Moreover, it has rejected Claims 1, 7, 8, 14-18, 27, 40, 46, 49, 50, 52 and 53 under 35 U.S.C. §102(a) as defining subject matter which is allegedly anticipated by Hackh's Chemical Dictionary. Further, it has rejected Claims 1-41, 49-50 and 52-59 under 35 U.S.C. §103(a) as defining subject matter which is allegedly rendered obvious by the teachings in Hackh's Chemical Dictionary. Further, claims 1-59 have been rejected for two different reasons under 35 U.S.C. §112, first paragraph for allegedly being non-enabling.

Applicants provide the following remarks, which, when considered with the comments hereinbelow is deemed to place the present case in condition for allowance. Favorable consideration is respectfully requested.

At the outset, applicants note that the Office Action has maintained the election of species requirement under 35 U.S.C. §121. The Office Action has noted, however, that "the scope of the generic concept embraced by the species has been expanded to exclude other related species that would render the elected species obvious and therefore unpatentable. Accordingly, Claims 1-59 are pending and will be considered too [sic] the extent they read on the elected species and it's [sic] generic concept." Page 2 of the Office Action.

Applicants respectfully request clarification thereof. The record is confusing at this juncture as the Office Action indicates that it has expanded the generic concept embraced by the species to "exclude" related species that would render the elected species obvious, on

the one hand, and then states that it is considering the elected species and its generic concept, on the other hand. It is to be assumed that the word "exclude" is incorrect, and that the Office Action meant include.

However, even with that correction, the record is still unclear as the Office Action has not identified the "generic concept". The identification of the generic concept becomes even more critical if the applicants file one or more divisional applications, as it is unclear as to what subject matter the Office Action has considered patentably distinct and thus, it is unclear as to the subject matter that is properly to be placed in a divisional application. Moreover, it is also unclear as to the scope of the claims which the Office Action has examined, making it difficult to fully respond to the issues raised in the Office Action. Thus, applicants respectfully request that the United States Patent and Trademark Office delineate the scope of the "generic concept" being examined to make the record clear.

Claim 1 has been amended to correct a grammatical error therein. Such an amendment does not narrow the scope of the claimed invention.

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached page is captioned "Version with markings to show changes made."

Pursuant to the rejection of Claims 42-48 and 51 under 35 U.S.C. §112, first paragraph, the Office Action alleges that the application is enabling for treating cancer; but alleges that it does not reasonably provide enablement for treating all cancers. However, the Office Action has not provided any evidence to support its allegation.

Applicants respectfully submit that the Office Action has not made a *prima facie* case of non-enablement. Case law has held that the PTO "has the initial burden to

establish a reasonable basis to question the enablement provided for the claim invention." *In re Wright* 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). Moreover, attention is directed to *In re Marzocchi*, where the court held that

> As a matter of Patent Office practice, then, a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented *must* be taken as in compliance with the enabling requirement of the first paragraph of § 112 *unless* there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support. ...
>
> [I]t is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain *why* it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement.

In re Marzocchi 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971).

In re Sichert reaffirms the requirement for "evidence or reasoning of record which is inconsistent with a critical statement in the disclosure" in order for a rejection under 35 U.S.C. § 112 to be proper. *In re Sichert* 566 F.2d 1154, 196 USPQ 209, 214.

Moreover, attention is directed to MPEP 2164.04, wherein it further states that "specific technical reasons are always required" to support a *prima facie* case of lack of enablement.

The Office Action however provided no evidence, nor any specific technical reasons, in support of the allegation that the claimed invention lacks utility under 35 U.S.C. §112. It failed to cite an article or publication that supported its allegation. It failed to provide any technical reason to support its allegation. It makes general allegations that cancer therapy remains highly unpredictable, but the Office Action has not found any specific evidence which refutes applicants' position that the compounds herein are useful for treating cancer. Such a position is inconsistent with case law and the MPEP, which the USPTO is bound to follow. Since the Office Action has not met the burden of establishing a *prima facie*

case of lack of enablement under 35 U.S.C. §112, applicants respectfully request withdrawal of the rejection made on this basis.

Moreover, the Office Action admits that the application is enabling for treating cancer. In fact, the application exemplifies using representative species that the compounds of the present invention inhibit cancer cells. For example, the application shows the effect of representative compounds on several different cancer lines, for example. Jurkak, LN Cap, MDA-361, PC-3, MDA-468, PC31, DU145, MDA-36, MCF-7, MIA PaCa-2, Hep G2, A549, NCI H460, HT-29, HCT-116, SK-OV3, that is, for example, prostate cancer cells, breast cancer cells, pancreatic cancer cells, liver cancer cells, lung cancer cells, colon cancer cells, ovarian cancer cells. (See Figures 2-40 and Examples 1-4,6, 7 and 8). In addition, attention is directed to Example 5, which provides data illustrating the effect of a representative compound on the proliferation of cancer cells using prostate cancer cells as representative of cancer. Finally, the application shows that the ability of these compounds to inhibit cancer proliferation results from the compounds of the present invention being T-like channel antagonists, that is, they retard and/or prevent the passage of calcium through calcium T-like channels into the cancer cell. See for example, Examples 9 and 10 of the instant application. As described in the application, it is believed that cancer cell proliferation is activated by calcium entry into the cell through the calcium T-like channel; by blocking or retarding the calcium entry, the compounds of the present invention retard cancer cellular proliferation. Thus, the specification contains scientific evidence that shows that the compounds are effective in treating cancer.

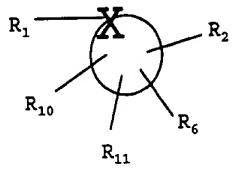
Applicants respectfully submit that the data in the application provides sufficient evidence to support the scope of the claimed subject matter.

Thus, for the reasons provided herein, the rejection of Claims 42-48 and 51 under 35 U.S.C. §112, first paragraph is overcome, withdrawal thereof is respectfully requested.

In support of the rejection of Claims 1, 7, 8, 14-18, 27, 40, 49, 50, 52 and 53 under 35 U.S.C. § 102(a), the Office Action cites Hackh's Chemical Dictionary. The Office Action alleges that the dictionary teaches the simplest species of the claims, furan, thiophene, pyrrole, etc.

However, contrary to the allegations of the Office Action, the compounds within the scope of the present invention are more complex than simple heterocyclics.

For example, the present invention is directed to inter alia, compounds of the formula



or pharmaceutically acceptable salts thereof wherein

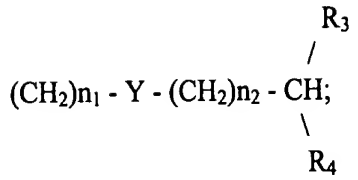
X is N or CH;

is a cyclic 5-10 membered cyclic ring which is saturated and which may contain 1 or 2 additional ring heteroatoms selected from the group consisting of O, S and N, with the remaining ring atoms being carbon atoms;

R_1 is (CH_2) n – Z –(R_5), Q, hydrogen or lower alkyl;

R_2 is hydrogen or Q';

Q and Q' may be the same or different and are independently



Z is a chemical bond, CH_2, O, S or NH;

Y is CH_2, O, S or NH;

R_3, R_4, and R_5 are independently cyclic rings containing 6-14 ring carbon atoms, and containing no hetero ring atoms, which cyclic rings may be completely saturated, partially unsaturated or aromatic, and which are unsubstituted or substituted with an electron donating group or electron withdrawing group;

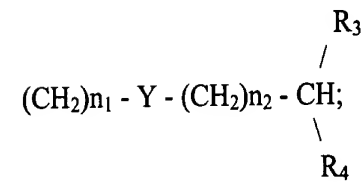
R_3 and R_4 may be fused to form a cyclic ring structure containing 12-28 carbon atoms;

R_6, R_{10} and R_{11} are independently hydrogen or lower alkyl, which is unsubstituted or substituted with an electron withdrawing group or electron donating group;

n_2 is 0-8; and

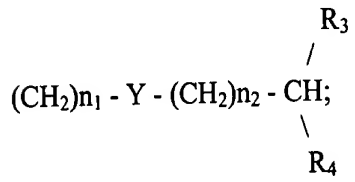
n and n_1 are independently 1-8, provided that either R_1 is Q or R_2 is Q'.

As clearly defined by the claims when it is stated that either R_1 or R_2 is Q or Q^1, the compounds of the present invention must contain, inter alia, a substiutent



wherein R_3 and R_4 are cyclic rings containing 6-14 ring carbon atoms, Y is CH_2, O, S, or NH and n_1 and n_2 are as defined hereinabove.

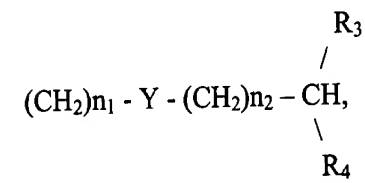
Thus, the claimed compounds encompass more than mere simple heterocyclics defined in the dictionary. For example, the compounds illustrated on page 38-41 of the specification are within the scope of the claimed invention. These compounds are much more complex than the simple heterocyclic moieties described in Hackh's Chemical Dictionary. Hackh's Chemical Dictionary does not teach or disclose heterocyclics substituted by the aforementioned substitutent



or the compounds illustrated on pages 38-41 of the instant specification. Thus, Hackh's Chemical Dictionary does not anticipate the claimed compounds.

Therefore, the rejection of Claims 1, 7, 8, 14-18, 27, 40, 46, 49, 50, 52 and 53 under 35 U.S.C. §102(a) is overcome; withdrawal thereof is respectfully requested.

Pursuant to the rejection of Claims 1-41, 49, 50 and 52-59 under 35 U.S.C. §103 the Office Action cites Hackh's Chemical Dictionary. Applicants reiterate the arguments hereinabove. As described hereinabove and recited in Claim 1, the present invention includes, inter alia, heterocyclic compounds substituted, by inter alia,



wherein the substituents are defined hereinabove. Hackh's Chemical Dictionary discloses simple heterocyclics, it does not teach, disclose or suggest compounds having, inter alia, the aforementioned substitutent thereon. Moreover, the Office Action has not indicated any

teaching in the chemical dictionary where such a compound is taught or disclosed or suggested.

Thus, for the reasons given, the rejection of Claims 1-41, 49, 50 and 52-59 under 35 U.S.C. §103(a) is obviated; withdrawal thereof is respectfully requested.

Pursuant to the rejection of Claims 1-59 under 35 U.S.C. §112, first paragraph, the Office Action alleges that the specification does not give any guidance as to how each of the heterocyclic substituted derivatives were prepared.

Applicants disagree. Attention is directed to page 21, line 17 to page 26, line 9 of the instant specification which generally describes the procedure for making the compounds of Formula I. Moreover, attention is directed to page 31, line 9 to page 37, line 25, which specifically illustrates the generalized description referred to hereinabove and utilizes this process for making the twenty-five compounds listed in Table I. Thus, the application provides sufficient direction and guidance, with exemplification for preparing compounds of Formula I which are claimed and recited in Claim 1. Thus, based on the teachings therein, one of ordinary skill in the art can make the compounds of Formula I including the heterocyclic substituted derivatives, without an undue amount of experimentation. Therefore, this rejection of Claims 1-59 under 35 U.S.C. §112, first paragraph is obviated; withdrawal thereof is respectfully requested.

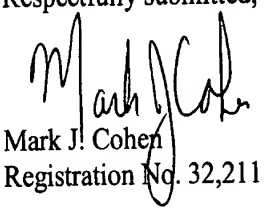
Pursuant to the rejection of Claims 1-59 under 35 U.S.C. §112, the Office Action alleges that he specification is not enabling for derivatives containing other than the 5-membered N-heterocyclic moiety. More specifically, the Office Action alleges that he specification does not provide enablement for the full scope of the claimed subject matter.

Applicants disagree. As described hereinabove, with respect to the arguments traversing the previous rejection, the contents of which are incorporated by reference, the specification describes with sufficient guidance for one of ordinary skill in the art to make the compounds within the scope of Formula I recited in the claims, and for making the specific species listed in Table I on pages 38-41 of the instant specification. Furthermore, looking at just the species disclosed in Table I, the compounds therein include derivatives which contain more than a 5-membered N-heterocyclic moiety. For example, species listed on pages 38-39 have a 6-membered heterocyclic moiety; thus, the application has exemplification of the synthesis of specific compounds which contain other than a 5-membered nitrogen containing ring. Moreover, the teachings on pages 21, et seq. provides sufficient guidance for one of ordinary skill in the art to make other compounds within the scope of the present invention.

Furthermore, the description on pages 26 et seq. teach one of ordinary skill in the art to make and use pharmaceutical compositions containing same for treating cancer. Furthermore, Figures 2, 3and 9 and examples 1-4, 6-8 provide in vitro evidence of the effectiveness of representative compounds of retarding or preventing the proliferation of various cancer cells using various representative compounds of the present invention. Further, Example 5 exemplifies in vivo evidence showing the use of a representative compound for retarding or preventing the proliferation of cancer cells. These exemplifications and teachings enable one of ordinary skill in the art to make and use the compounds of Formula I, regardless of the definitions X, R_3, R_4, R_5 or heterocyclic, as defined in accordance with the present invention, without an undue amount of experimentation. Therefore, the rejection of Claims 1-59 under 35 U.S.C. §112, first paragraph is obviated; withdrawal thereof is respectfully requested.

Thus, in view of the Remarks hereinabove, it is respectfully submitted that the present case is in condition for allowance, which action is earnestly solicited.

Respectfully submitted,



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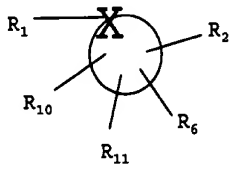
"VERSION WITH MARKINGS TO SHOW CHANGES MADE"

IN THE CLAIMS:

Please amend Claim 1 as follows:

1. (Twice Amended) A compound of the formula:



[and] or pharmaceutically acceptable salts thereof wherein

X is N or CH;

is a cyclic 5-10 membered cyclic ring which

is saturated and which may contain 1 or 2 additional ring heteroatoms selected from the group consisting of O, S and N, with the remaining ring atoms being carbon atoms;

R_1 is (CH_2) n – Z –(R_5), Q, hydrogen or lower alkyl;

R_2 is hydrogen or Q';

Q and Q' may be the same or different and are independently

$$(CH_2)n_1 - Y - (CH_2)n_2 - \underset{\displaystyle R_4}{\overset{\displaystyle R_3}{CH}};$$

Z is a chemical bond, CH_2, O, S or NH;

Y is CH_2, O, S or NH;

R_3, R_4, and R_5 are independently cyclic rings containing 6-14 ring carbon atoms, and containing no hetero ring atoms, which cyclic rings may be completely saturated, partially unsaturated or aromatic, and which are unsubstituted or substituted with an electron donating group or electron withdrawing group;

R_3 and R_4 may be fused to form a cyclic ring structure containing 12-28 carbon atoms;

R_6, R_{10} and R_{11} are independently hydrogen or lower alkyl, which is unsubstituted or substituted with an electron withdrawing group or electron donating group;

n_2 is 0-8; and

n and n_1 are independently 1-8, provided that either R_1 is Q or R_2 is Q'.